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Anh Nguyen
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To: NCIC HPV@EPA
cc:
Subject: Environmental Defense comments on Alkyl-substituted Cyclohexanol Derivatives

----- Forwarded by Anh Nguyen/DC/USEPA/US on 12/22/2003 02:01 PM -----

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Subject: Environmental Defense comments on Alkyl-substituted Cyclohexanol Derivatives

(Submitted via Internet 12/22/03 to oppt.ncic@epa.gov, hpv.chemrtk@epa.gov, boswell.karen@epa.gov, chem.rtk@epa.gov, lucierg@msn.com and tadams@therobertsgroup.net)

Environmental Defense appreciates this opportunity to submit comments on the robust summary/test plan for Alkyl-substituted Cyclohexanol Derivatives .

This test plan and robust summaries were submitted by the Cyclohexyl Derivatives Consortium under the auspices of the Flavor and Fragrance High Production Volume Consortia. It is comprised of two HPV chemicals; 4-tert-butyl cyclohexanol (TBCH, CAS# 98-52-2) and 4-tert-butylcyclohexyl acetate (TBCHA, CAS# 32210-23-4). These substances are used primarily as fragrances in soap. Therefore, environmental and human exposures are assumed for both TBCH and TBCHA. No information was provided on the magnitude of exposures that are likely to occur.

We agree that TBCH and TBCHA belong in a category. TBCHA is readily converted to TBCH by carboxylesterases present in most biological systems and all other available data are consistent with the proposal to place TBCH and TBCHA in a category.

The sponsor also proposes to use surrogate data from 2-isopropyl-5-methyl cyclohexanol (IPMCH) to fulfill SIDS requirements for reproductive, developmental and in vivo genetic toxicity studies. We disagree with this proposal because the justification is far from adequate. The stated basis for the use of surrogate data is that TBCH, TBCHA and IPMCH all are excreted as glucuronide conjugates and that they have similar LD50 values in rodents. However, many synthetic or endogenous agents are excreted as glucuronides, yet possess vastly different patterns of toxicity. Examples include DES, some PCBs, testosterone, naphthol, bilirubin, p-nitrophenol, benzo(a)pyrene and other polycyclic aromatic hydrocarbons and chlorobenzenes. Likewise, many agents have acute toxicity values around 4000 mg/kg, yet they certainly do not belong in the same category. Moreover, IPMCH may cause a different pattern of toxicity because of the presence of a methyl group on the ring structure. After all, toluene and benzene do not belong in the same category, although they differ structurally only by a methyl group on the phenyl ring. For the above reasons, we recommend that the proposal to use IPMCH as a surrogate be abandoned and that a combined reproductive/developmental study be conducted on either TBCH or TBCHA. An in vivo genetic toxicity study may not be needed because of the availability of multiple in vitro tests on both TBCH

and TBCHA that demonstrate that these substances are not genotoxic.

Other comments are as follows:

1. TBCH and TBCHA are readily biodegradable and should not bioaccumulate.

2. Available aquatic toxicity data are sufficient to fulfill HPV requirements and demonstrate that these agents possess low to moderate aquatic toxicity.

3. Repeat dose studies involving TBCH indicate some neurological toxicity; these studies are adequate for read-across to TBCHA.

4. The repeat dose study on TBCH indicated an effect on epididymis weights. This finding adds further justification for our conclusion that a reproductive/developmental study is needed for either TBCH or TBCHA.

5. We are puzzled that the test plan spends several pages attempting to discount the significance of hyaline droplet formation in male rat kidneys after TBCH or IPCMH exposures. This discussion is really not relevant to HPV requirements, as it is a risk assessment issue. Moreover, nearly all of the discussion is directed towards other chemicals such as d-limonene, gasoline additives, decalin, isophorone and others not relevant to this test plan on TBCH or TBCHA.

6. If the sponsor wishes to pursue the use of IPCMH as a surrogate, we recommend that gene expression arrays be generated in an appropriate biological system. If the arrays reveal that IPCMH causes a pattern of gene expression changes similar to TBCH or TBCHA, this would constitute strong evidence for a common mode of biological and toxicological properties.

Thank you for this opportunity to comment.

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